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13. ABSTRACT *(Maximum 200*

This is a Career Development Award which provides salary support for research and training done under a separately-funded project, Grant Number DAMD 17-94-J-4475 (P.I. Dr. James R. Hebert), called the **B**reast **R**esearch **I**nitiative for **D**eterminin**G** **E**ffective **S**kills (BRIDGES), which focuses on skills for coping with breast cancer, and consists of a prospective randomized intervention trial with women ages 65 or less, having stage 1 or 2 breast cancer, randomized to one of three arms: 1) a modified form of the University of Massachusetts Medical Center mindfulness meditation-based Stress Reduction and Relaxation Program (SR&RP); 2) a nutrition education program developed specifically for BRIDGES; and 3) a usual-care control group. Outcome parameters are: 1) psychological and behavioral indices of function and coping; 2) quality of life measures; 3) compliance with the interventions and medical treatment regimens; and 4) immunological/endocrinological measures consisting of cytokines and melatonin. Over the past year, I have been involved in the following aspects of the project: design planning, recruitment, providing part of the SR&RP intervention, writing manuscripts, serving on the Executive and Steering Committees, data analysis, and overseeing sample collection and analysis for the melatonin assays. In addition, I attended extra training programs related to the SR&RP intervention.

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FOREWORD

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M.D. 10-29-96

PI - Signature Date

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INTRODUCTION

This four-year Career Development Award provides me with salary support for a training practicum done as part of a separately funded research project, Grant # DAMD17-94-J-4475 titled "Effects of Meditation-Based Stress Reduction in Younger Women with Breast Cancer". The study is called the **B**reast **R**esearch **I**nitiative for **D**eterminin**G** **E**ffective **S**kills (BRIDGES), focusing on effective skills for coping with breast cancer. The Principal Investigator for that project, James R. Hebert, MSPH, Sc.D., is my mentor on the Career Development Award. Please note that my application for this award was originally written in association with another project application which was not funded. Therefore, the original Statement of Work provided with the Career Development Award application has changed to correspond with the work done for the funded project. A revised Statement of Work is included here. It is structured according to the timeline for the project. The results of the project are included in Dr. Hebert's annual report. I have extracted portions of that report which apply to the work I have done.

Following is a summary of the background and overall goal for my Career Development Award. The background is extracted from the project grant. Also included are the specific aims and hypotheses from the project grant.

Background

An increasing body of research literature has shown that psychological states have clear impact on recovery and quality of life in women with breast cancer. Psychosocial variables such as emotional expression, coping style, and factors related to social support appear to have the most promise for improving quality of life and increasing the probability of prolonged survival. Also, there is a small body of evidence indicating that women with breast cnacer receiving psychosocial interventions may derive a beneficial effect in respect to improved response and disease-free survival.

In light of these findings, there is an important need for the development of cost-effective psychosocial interventions for women with breast cancer. A successful intervention will be one that can reduce emotional distress, promote effective coping, and be useful and adaptable to the diverse population of women with breast cancer. The BRIDGES study seeks to adapt the University of Massachusetts Medical Center's Stress Reduction and Relaxation Program (SR&RP) for women with breast cancer. The SR&RP is a well-established intervention program with demonstrated effectiveness in improving emotional status and quality of life in individuals with a variety of serious medical problems. The program is educational in format. It has been offered to diverse populations, including a general hospital settings, an inner city clinic and a prison population.

The BRIDGES study addresses aspects of two of the fundamental research issues in psychosocial aspects of breast cancer: 1) the psychosocial impact of breast cancer, particularly on quality of life and ability to cope; and 2) identifying techniques for delivering

cost-effect care to facilitate recovery, improve quality of life, and possibly improve immune response after receiving a diagnosis of breast cancer. The study is designed to evaluate the effectiveness of the SR&RP, previously untested in this population of patients, and compare it to a usual-care group as well as a nutrition education program which is an inactive attention control relative to the SR&RP but may have active therapeutic aspects as well.

Overall goal of the Career Development Award

My overall goal is to investigate a well-established short-duration psychosocial intervention, the University of Massachusetts Medical Center (UMMC) SR&RP for use with women with breast cancer. Outcome measures of particular interest are those relating to adjustment to illness, quality of life, ability to comply with medical recommendations, immune parameters related to tumor surveillance and potentially to the intervention, and an endocrine parameter, melatonin, which is believed to be an oncostatic agent involved in the immunological response to breast cancer and may potentiate the response to chemotherapy, thus representing a biologic predictor of good prognosis. My particular focus is on the psycho-physiologic interactions involved in coping with breast cancer, and on using the associated outcome measures to test the study hypotheses. This goal is achieved by working on the BRIDGES research project as a practicum experience. My mentor is Dr. James R. Hebert, the Project P.I. As noted above, the project is separately funded by your agency.

Specific Goals of the Career Development Award:

To gain experience and training in the following aspects of conducting this kind of research, which is a trial of a randomized psychosocial clinical intervention using psychosocial and biological outcome parameters: 1) research study design; 3) start-up planning; 4) recruitment; 5) delivering the intervention(s); 6) data collection and analysis; 7) hypothesis testing; and 8) reporting results via manuscripts.

Overall Goal of the BRIDGES study

The primary goal of this study is to test the efficacy of the well-established short-duration mindfulness meditation-based Stress Reduction and Relaxation Program (SR&RP) in women 65 years or less who have stage I or II breast cancer diagnosed within the past two years. The SR&RP intervention aims to influence a number of well-defined psychosocial factors which are suggested by a growing body of evidence as critically important for adjustment to ta potentially life-threatening diagnosis: enhancement of quality of life and potentially enhancement of resistance to disease progression and survival in women with breast cancer. The study consists of a prospective randomized three-arm design with a target goal of 60 women enrolled into each arm: 1) the SR&RP intervention, tailored to focus on issues specific to breast cancer; 2) a nutrition education program which will serve as an inactive attention control with regard to the psychosocial outcome measures and as a potentially active intervention with regard to effect on some outcome measures, such as immune parameters (see Aim 2); and 3) a usual-care control group.

Specific Aims and Hypotheses of the BRIDGES study

Aim 1: to test the effect of the SR&RP on quality of life (QOL), emotional awareness and expression, coping strategies and related perceptual and behavioral factors, and compliance with the intervention and medical treatment recommendations in women ≤ 65 years who have been diagnosed with Stage I or II breast cancer within the past two years. Because the SR&RP and NEP groups will have an equivalent time committment and the NEP will provide none of the essential components of the SR&RP, we will be able to examine the effect of the SR&RP intervention as distinguished from non-specific group/therapist factors.

> Primary Hypothesis: the SR&RP intervention will result in improved QOL and ability to cope, compared to either the NEP or usual care alone.
>
> Secondary Hypothesis: the SR&RP intervention will result in : a) improved perception of self and self in relationship to the world, as measured by increased self-esteem, sense of coherence, and decreased loneliness; b) a corresponding reduction in mood disturbance (e.g., anxiety and depression); c) increased use of active-behavioral and active-cognitive coping strategies, as measured by the Dealing with Illness Coping Inventory; and d) increased compliance with treatment regimens as compared to usual care alone.

Aim 2: to test the relative effect of the SR&RP versus NEP and usual care on endocrine/immune parameters specifically related to cytokines that activate Natural Killer (NK) cells and melatonin levels, which may in turn affect the response to breast cancer. Because NK activity may be related to recurrence, we have previously shown that low-fat diets enhance NK activity (Hebert, 1990) and we have preliminary data that meditation may affect melatonin levels (Massion *et al.*, 1995). Therefore, we are particularly interested in the relative differences between the two intervention groups, SR&RP and NEP, relative to usual care alone.

> Specific Hypothesis: Relative to usual care, the SR&RP intervention will be associated with enhanced immune responsiveness and enhanced melatonin levels in women with Stage I or II breast cancer enrolled in this study. This will be reflected by an increase in the production of cytokines, e.g. Interleukins 2 and 4, which activate NK cells, and Interferon, which activates macrophages, and melatonin levels as measured by the primary urinary melatonin metabolite, 6-sulfatoxymelatonin.

Aim 3: to determine if the study effects (described in Aims 1 and 2), along with maintenance of the intervention practices, persist over 1-2 years of follow-up.

> Specific Hypothesis: psychosocial and immunological changes will be maintained over time and related to on-going practice of the SR&RP self-regulatory strategies and behaviors, and NEP dietary practices.

REVISED STATEMENT OF WORK

Task One: Run-in Phase, Months 1-3

a, Conduct additional focus groups and preliminary data as needed. Analyze preliminary data previously gathered in support of this study.

b. Based on focus group interviews and preliminary studies, the existing SR&RP intervention will be adapted and expanded so that the content of the program will be most useful to women with early stage breast cancer.

c. Participate in finalizing and pilot-testing instrument materials.

d. Develop the protocol for collection of 24-urine samples for the melatonin assays and for analyzing the results of the assay. Work with the laboratory technician who is performing the assays and the Project Director, Susan Druker, to ensure that transportation of specimens and the assay procedure will be operational. Using samples conducted for a preliminary study, test out the assay procedure. Work with Dr. Hebert and the study biostatisticians on data analysis of the results. This process includes developing a familiarity with the technical aspects of conducting this assay and possible confounding variables, such as oral agents which elevate melatonin levels.

e. Participate in developing and creating the recruitment videotape and other recruitment materials (e.g. brochures) along with Drs. James Hebert, Judith Ockene, Jon Kabat-Zinn, and the Project Director, Susan K. Druker.

f. Develop the recruitment protocol, along with Drs. Hebert, Kabat-Zinn, Clemow, and the Project Director, Susan Druker.

g. Participate in training the Site Coordinators who will be conducting telephone and in-person interviews of the subjects. This will be done with Dr. Lynn Clemow, Co-Principal Investigator, and the Project Director, Susan Druker.

h. Participate in setting up the database and analysis of run-in phase data, along with Dr. James Hebert and the biostatisticians on the project.

Task Two: Recruitment, Months 4-21:

a. Serve as a member of the Executive Committee, composed of myself, Dr. Hebert, and Susan Druker, Project Director, to track the recruitment process and deal with any issues that may arise. Investigate any potential new recruitment sites as needed. This working group meets monthly to bi-monthly and functions to oversee the progress of the study, deal with administrative issues, and make decisions about issues that arise. An additional task will be

to work on maximizing opportunities for recruiting subjects and improving the effectiveness of the process.

b. Serve as a member of the Steering Committee, which meets quarterly and is attended by nearly all personnel involved in the study. These meetings are held to make some study decisions and maintain communication and cohesiveness among study personnel.

c. Provide consultation and supervision as needed to Susan Druker and the Site Coordinators during the recruitment process.

Task Three: Intervention, Months 6-27

a. Provide the six "booster" or "wrap-around sessions as part of the modified SR&RP intervention. These 6 sessions occur one before and five after the standard 8 week SR&RP program given at UMMC.

b. Take a two-month internship training program in giving the SR&RP as an intervention. This is provided by the Stress Reduction Clinic at UMMC, under the direction of Saki Santorelli, EdD.

c. Follow the progress of the nutrition education program (NEP) through the Executive and Steering committee meetings, where the nutritionist who gives the NEP will present progress reports.

d. Continue to serve on the Executive and Steering Committees to deal with ongoing study decisions and issues.

Task Four: Follow-up, months 8-46

a. Continue to oversee the melatonin sample collection and assay, as well as storage of samples, along with Susan Druker, Project Director.

b. Participate in tracking ongoing data collection, validating the data according to each individual instrument, and begin preliminary testing of study hypotheses.

c. As noted above, continue to oversee study progress by serving on the Executive and Steering Committee meetings, and being involved in administrative/study decisions.

Task Five: Final Data Analysis, months 47-51 (49-51 are a no-cost extension)

Along with Drs. Hebert and Clemow and the study biostatisticians, the following tasks will be done:

a. Participate in performing exploratory analyses to test for adherence to model assumptions.

b. Participate in testing study hypotheses.

c. Participate in conducting post-hoc analyses of study data.

d. Work with other study investigators and personnel in preparing manuscripts.

WORK ACCOMPLISHED

Task One: Run-in Phase, Months 1-3

a. Conduct additional focus groups and preliminary data as needed. Analyze preliminary data previously gathered in support of this study and in preparation for the study.

A preliminary focus group was conducted with a community-based breast cancer support group in order to gather data that would inform certain decisions such as timing of recruitment, and timing and length of the intervention itself. I conducted the focus group with another co-Principal Investigator. This data was then used in developing the recruitment protocol as well as the intervention protocol.

b. Based on focus group interviews and preliminary studies, the existing SR&RP intervention will be adapted and expanded so that the content of the program will be most useful to women with early stage breast cancer.

I was involved in the development of the modified SR&RP intervention, which consisted of adding 6 additional sessions, one session before and five after the standard SR&RP program which is 8 weeks long. The 8 sessions, provided as part of the standard stress reduction program already offered at the University of Massachusetts Medical Center, are larger groups composed of 30-40 people with a wide variety of medical or psychiatric problems, not just breast cancer. The 6 sessions were "wrapped around" the standard program and were given only to the women in the BRIDGES study. These were small group sessions composed of 6-12 women. The purpose of these sessions is to reinforce the practices taught in the program and give the women a chance to talk about issues specific to breast cancer.

c. Participate in finalizing and pilot-testing instrument materials.

I was involved in developing sections of the baseline questionnaire, particularly pertaining to medical and psychiatric information, as well as finalizing the acquisition and preparation of the all of the psychosocial instruments for use in the study.

d. Develop the protocol for collection and of the 24-urine samples for the melatonin assays and for analyzing the results. Develop a familiarity with the technical aspects of conducting this assay and any possible confounding variables, such as oral agents which elevate melatonin levels.

I researched and developed the procedure for collection of 24-hour urine specimens, delivery of the specimens to the laboratory which is conducting the melatonin assays for the study, storage of specimens, and data analysis of the results. Also, I oversaw a trial run of assays which was conducted by the laboratory using samples from a preliminary study which I

conducted with another co-investigator. This included working with the laboratory technician and Project Director to ensure that the assay procedure was feasible and to resolve any potential problems with it. I continue to oversee any issues which arise in relation to the assay and sample collection for it. This includes checking the results and monitoring for any factors which might confound the results (such as oral agents which elevate melatonin levels).

e. Participate in developing and creating the recruitment videotape and other recruitment materials (e.g. brochures), along with Drs. James Hebert, Judith Ockene, Jon Kabat-Zinn, and the Project Director, Susan Druker.

I attended weekly meetings during the first approximately 6 months of the study. The meetings were attended at various times by site coordinators from the four participating sites, the Principal Investigator, Project Director, and other investigators. I also chaired or participated in sub-committees involved in: 1) developing screening questions and baseline questionnaires to be used in recruiting and at the baseline assessment; 2) writing the script for the recruiting videotape and being involved in producing the videotape which was then used at the participating sites; 3) writing and producing other recruitment materials such as the brochure and descriptions of the individual interventions themselves; and 4) developing the actual recruitment procedure with specific modifications for each site.

f. Develop the recruitment protocol, along with Drs. Hebert, Kabat-Zinn, Clemow, and the Project Director, Susan Druker.

As part of the developing the recruitment protocols, I researched the effectiveness of recruitment methods used in other studies similar to our and contacted other investigators involved with those studies who were able to provide valuable information. I was part of a working group, composed of Dr. Hebert and the Project Director, Susan Druker, which developed the procedure for recruiting subjects at each of the study sites. I had the specific task of researching recruitment strategies which were specific for two of the sites, Medical Center of Central Massachusetts and Fallon Clinic. This involved interfacing with the various medical/surgical specialty clinics involved in seeing women with breast cancer, as well as the departments involved in keeping databases which could identify potential subjects for the study. I worked with Susan Druker on integrating all of the strategies for all the sites in the study.

Also, I was involved in developing the screening questionnaire used during the recruitment process.

g. Participate in training and supervising the Site Coordinators who will be conducting telephone and in-person interviews of the subjects. This will be done with Dr. Lynn Clemow, Co-Principal Investigator, and Susan Druker, Project Director.

I was involved in supervising and training Susan Druker and the Site Coordinators in

developing the procedures for telephone and in-person interviews, along with Dr. Clemow. Also, I continue to be available for on-going consultation in screening and other clinical issues as needed.

h. Participate in setting up the database and analysis on run-in phase data, along with Dr. James Hebert and the biostatisticians on the project.

I have been involved in setting up the database and conducting process-related analyses (to ensure that data collections steps have occurred) and simple univariate analyses, under the supervision of Dr. Hebert and along with the study biostatisticians. I attend regular data analysis meetings to set up and develop the database and database management plan.

Task Two: Recruitment, Months 4-21

a. Serve as a member of the Executive Committee, composed of myself, Dr. Hebert and Susan Druker, Project Director, to track the recruitment process and deal with any issues that may arise. Investigate any potential new recruitment sites as needed. Work on maximizing opportunities for recruiting subjects and improving the effectiveness of the recruitment process.

I have performed this task as described above. These meetings will be ongoing throughout the study. One of the decisions made by the committee, after consulting with other study investigators, was to raise the age inclusion criteria to extend to women ages 65 or less. The rationale for this decision is explained in Dr. Hebert's report. Also, we extended the criteria for period of diagnosis to include women diagnosed within the past two years.

During 1995-1996 I explored options for other potential recruitment sites, particularly at three facilities in the nearby area. I was responsible for all of the initial contact work with the physicians and appropriate personnel at those facilities. I went with Dr. Hebert and the Project Director, Susan K. Druker, to make presentations at two of the facilities and meet with personnel who would be involved in recruiting. The two facilities, Burbank Hospital (an affiliate of UMMC and Bay State Medical Center in Springfield, MA., have agreed to informally recruit subjects for the study. The decision was made to leave the agreement informal rather than set up formal sub-contract sites.

As of 10-29-96, 165 women have been recruited into the study and 11 have dropped out. Our projected goal is 180 women in the study, 60 in each study arm.

b. Serve as a member of the Steering Committee, which meets quarterly and is attended by nearly all personnel involved in the study. These meetings are held to make some study decisions and maintain communication and cohesiveness among study personnel.

I have been involved in planning and participating in quarterly Steering Committee meetings

as described above. These meetings will be ongoing throughout the study.

Task Three: Intervention, months 6-27:

a. Provide the six "booster" or "wrap-around sessions as part of the modified SR&RP intervention. These 6 sessions occur one before and five after the standard 8 week SR&RP program given at UMMC.

During the first intervention cycle, I and another co-investigator provided the 6 "wrap-around" or booster sessions for the women randomized to the stress reduction intervention arm. Beginning with the second intervention cycle, I began providing the 6 sessions alone and will continue to do so for the remaining intervention cycles. These 6 sessions occur before and after the standard stress reduction program, as explained above. Five intervention cycles have been completed or are in progress, each lasting 14 weeks total (8 standard sessions plus 6 "wrap-around" sessions). A sixth intervention will be offered beginning in January 1997. In general, the women have been reporting that the intervention has been quite beneficial.

b. Take a two-month internship training program in giving the SR&RP as an intervention. This is provided by the Stress Reduction Clinic at UMMC, under the direction of Saki Santorelli, EdD.

I took a two-month training program in giving the SR&RP as an intervention and am involved in two other on-going training programs which are related to stress reduction methods. These latter programs meet for 2-4 days approximately 3-4 times a year.

c. Follow the progress of the nutrition education program (NEP) through the Executive and Steering committee meetings, where the nutritionist who gives the NEP will present progress reports.

I am aware of the progress of the nutrition education program (NEP) through the regular Executive Committee meetings and Steering Committee meetings, where the nutritionist who gives the NEP presents progress reports.

d. Continue to serve on the Executive and Steering Committees to deal with ongoing administrative study decisions and issues.

As noted above, these are ongoing meetings. The study is primarily administrated by virtue of the functioning of the Executive Committee, a working committee composed of myself, Dr. Hebert, and Susan Druker, the Project Director. Dr. Clemow and the study biostatisticians also attend as needed.

Task Four: Follow-up, months 8-46

a. Continue to oversee the melatonin sample collection and assay, as well as storage of samples, along with Susan Druker, Project Director.

This is being done as described. The assays are done in a batch when approximately 50 samples have been accumulated.

b. Participate in tracking ongoing data collection, validating the data according to each individual instrument and begin preliminary testing of study hypotheses.

Currently, I and other members of the research group are involved in validating the data according to each individual instrument to make sure that the data makes sense and is consistent. Also, along with Dr. Hebert and the study biostatisticians, I am involved in conducting descriptive, univariate data analyses and preliminary testing of study hypotheses

c. As noted above, continue to oversee study progress by serving on the Executive and Steering Committee meetings, and being involved in administrative/study decisions.

This is being done as described above.

Task Five: Final Data Analysis, Months 47-51

Along with Drs. Hebert and Clemow and the study biostatisticians, the following tasks will be done:

a. Participate in performing exploratory analyses to test for adherence to model assumptions.

b. Participate in testing study hypotheses.

c. Participate in conducting post-hoc analyses of study data.

d. Work with other study investigators and personnel in preparing manuscripts.

Because we are not yet at this stage of the study, there has been no activity except for preparing some manuscripts based on preliminary data gathered prior to starting BRIDGES and one book chapter which includes some preliminary melatonin data:

Previously, I co-authored a paper reporting on preliminary data gathered prior to submitting the original grant application (Massion *et al.* 1995) in which we discussed one of the study hypotheses, namely that the SR&RP intervention would be associated with enhanced melatonin levels.

During the past year, I co-authored a second paper on another preliminary study conducted prior to the BRIDGES study, which related to and supported the same hypothesis. That study is in submission and has not been published yet. Also during the past year, I co-authored two

book chapters, both of which discussed the BRIDGES study. The first chapter (Kabat-Zinn *et al.*, 1997) discussed the use of the SR&RP intervention as an intervention for cancer patients. The chapter was primarily descriptive and briefly mentioned BRIDGES. No data were presented.

The second book chapter discussed our hypothesis about meditation and melatonin. BRIDGES was discussed and preliminary data on melatonin levels from 82 subjects at baseline and 4-month follow-up (approximately 2-3 weeks after the intervention) was presented: crude mean difference for each group in μg per 24 hours, with the standard deviation of the difference (not the overall standard deviation) shown in parentheses was: SR&RP = +1.58 (11.87); NEP = +3.26 (9.03); and usual-care = -1.06 (10.30). Note that the standard deviation of the difference is approximately 1½ times as large as the standard deviation for the cross-sectional difference.

Due to the large variability in the data, the overall effect was not statistically significant ($p = 0.33$), nor was the effect due to either of the interventions relative to usual care: NEP ($p = 0.15$) and the SR&RP ($p = 0.34$). However, we believe the results are suggestive because they were obtained in a randomized trial where background factors are controlled by design and in which we would expect less of an effect than in a highly self-motivated group of experienced meditators - hence more relevance to the experience of average people. Also, these results were obtained on less than half of the projected sample and cover only the first four months. There will be a third melatonin assay done at the two-year point.

Both chapters are still being edited and therefore are not included here.

None of the other data are ready to be analyzed yet because we are in month 24 of the project. For quality control reasons, the immunological assays will not be done until the third year of the project.

CONCLUSIONS

In general, my experience working on the BRIDGES study as a practicum for the Career Development Award has been excellent. I have been involved in a substantial portion of the project at every stage of progress, and have had direct impact on the majority of the major decisions and design issues. The training and experience I am receiving can be generalized to other clinical psychosocial interventions with psychosocial and biological outcome parameters.

As a group, we have been successful in recruiting close to 90% of our targetted total for subjects, with only 6% dropping out. The work accomplished has closely adhered to the Statement of Work outlined in the project grant.

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